01/09/2019

Re: Findings from CRU (Psychiatry) Review of Pro000095555 (Received on 01.07/2019)

We are thankful to the Psychiatry CRU for their further examination on the REMIT study (Pro00005555). We have thoroughly reviewed the report and we offer the following responses in order to clarify several issues raised by our CRU examination. These responses are in italic text.

Issues in **Table 3. Reasons for Not Meeting Eligibility Criteria**

EC 1 090-024 Patient had a cardiac catheter and unstable angina in the last 3 months as per the 1st week of July discharge summary.

This patient was enrolled to REMIT study as he has not had re-vascularization procedure and his chest symptoms were not considered due to coronary artery blockage. The discharge summary noted that he was hospitalized on Duke Cardiology inpatient service between 06/27/2008 and 07/01/2008 for concern of "Unstable angina". He was found having no acute myocardial infarction. He underwent a diagnostic cardiac catheterization on 06/30/2008 without any re-vascularization. He also was found having normal LV function. He received PPI and discharged after ambulating several times in the halls without shortness of breath or chest discomfort. His cardiologist, Dr. Blazing, felt the patient's IHD was stable and agreed to have the patient being enrolled to REMIT study.

EC 4 299-098 The patient did not hold his beta blocker because he forgot. The visit was conducted as planned. The patient died on 12/1/2010. Week 5 phone visit was Nov 4th. Finished 6 weeks. The study team became aware of the death on 3/29/11 as the print out of the obituary is dated 3/29/11. They officially noted this at the 1-year follow-up on 9/23/2011. He was in the follow-up phase when he died. The death was not reported to the IRB. Cause of death cannot be determined as there is no documentation. The patient was 68 years old at the time of death.

REMIT study was to report the death and other SAEs that occurred during the 6-week intervention trial to IRB.

EC 10 025-012 Did not meet criteria due to history of lung cancer which metastasized to the brain. The patient dropped out due to cancer spreading to the brain and did not get study intervention.

Six days after completing the REMIT baseline stress testing and after randomization to REMIT intervention, this patient had a dizzy spell and was found to have a brain lesion thereafter.. The diagnosis of brain metastasis from lung cancer was made days later. There was no evidence that this patient had a lung cancer prior to his dizziness event.

EC 12 144-042 As per study notes, patient had depression and takes daily amitriptyline.The participant source documents by the CRC mention that the patient plans to discontinue amitriptyline, but we did not find any documentation confirming this (med logs etc.). We cannot confirm if it was a current med list form the notes.

This patient was taking amitriptyline 25mg daily for his neuropathic pain. Per the REMIT study coordinator, the patient discontinued this medication prior to the baseline assessment.

EC 6 and EC 12 265-090 Patient was admitted for chest pain 2 weeks prior to randomization.

Patient found to be depressed during hospitalization and started on fluoxetine prescribed by Dr. Jiang. After discharge, she remained on fluoxetine. She is also a WOCBP, but no pregnancy test was completed and she does not have a hysterectomy or any other permanent contraception.

This patient was admitted to Duke Cardiology inpatient service for observation due to recurrent chest pain after she provided consent to REMIT study prior to the baseline assessment. Psychiatry consult was called to address the patient's depression and fluoxetine was recommended by the resident doctor who was on service with Dr. Jiang, the REMIT PI. Dr. Jiang obtained confirmation from the patient who insisted on continuing with the REMIT study (Clinical note can be found in Maestro). Therefore, the patient did not take fluoxetine.

Issues in **Table 5. Other Concerns Regarding Participant Eligibility**

236-081 The patient died during study. As per our review, this subject was ineligible. It was noted that he was unable to perform the stress test as he walked with a cane. The patient was randomized and received active study drug. Patient was rated as a study drop after his death on 4/30/2010. The last follow-up on study was a week 4 phone call on 4/22/10. On week 5, the study team found out that the patient was dead due to a significant renal disease (cr = 3.4 in

October of 2009). There was a discussion of putting the patient on dialysis during their participation in the study.

The REMIT team was aware of the discussion about the patient may begin dialysis in the future as the cardiologist noted on 02/18/2010) "We did discuss that with his worsening renal insufficiency, he would be a high risk for requiring dialysis sooner than later if we did cath him. We will go ahead and let his dialysis access issues be sort out before we consider any further intervention for his peripheral arterial disease at this time. It sound like he has seen the vascular surgeon at the VA and they are planning to place an AV fistula at sometime here in the near future". When this patient was enrolled to REMIT, there was no plan for him to have the AV fistula to be placed. Renal insufficiency with Cr. 3.4 was not an exclusion criteria of REMIT.

296-096 Patient is eligible. However, he received a prescription for Lexapro from Dr. Jiang at his primary endpoint visit. Lexapro is also the study drug (i.e., escitalopram). Blind was broken for all study subjects when the last subject completed the last primary endpoint. There is also no information on when the patient was supposed to fill the prescription.

The patient requested to take Lexapro after he/she completed the 6-week REMIT intervention regardless of whether he/she received drug or placebo during the triall. Neither the PI, other team members, nor the patient knew whether he/she was taking Lexapro or placebo.

Issues in **PROTOCOL VIOLATIONS**

It was noted that 6 manuscripts have been published using data from those patients (N=307) who completed the baseline eligibility assessment. However, the approved protocol or informed consent form (ICF) does not state that this baseline assessment data, among those patients who do not go on to participate in the REMIT RCT, will be used in this manner.

It has been our belief that, as long as there is no additional risk to study participants, we can work on data collected from IRB approved studies for explorative purposes that were not specifically listed in the primary protocol. We would no doubt to comply to guidelines regarding this measure if they are available.

Moreover, the most recent published manuscript reviewed (published in 2017) reported annual longitudinal findings from this baseline sample for a median of four years. Information collected included patient's medical status, hospitalizations, and current use of antidepressant medication. For patients who could not be reached after telephone call attempts, information was gathered from medical records. This publication also states that "The study protocol was reviewed and approved by the Duke Institutional Review Board, and all participants provided written informed consent." However, this schedule of assessments is not listed in the approved protocol or the study informed consent form (ICF). Again, the ICF only outlines a schedule of events for those patients who participate in the REMIT RCT.

It was my oversight that the sentence regarding the long-term follow-up, i.e. "Also, patients will be followed yearly until the last patient enrolled completes his or her 3 year follow-up." was misplaced in the section of the protocol describing the treatment phase of the study. This sentence should have been in in a separate paragraph as this follow-up was applied to all REMIT participants who completed the baseline stress testing. All the REMIT team members, including PI, co-investigators, and research staff members, were fully aware long term follow-up was to occur for all REMIT participants regardless whether they had been randomized. This follow-up goal was verbally delivered to the REMIT participants when they provided the study consent.